b) maintaining the membrane at the predetermined temperature for a period of time of from about 1 to 250 hours; and

c) incorporating said membrane into a controlled drug delivery device.

[00029] These and other aspects, features, and advantages of this invention will be more apparent from the following detailed description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[00030] FIG. 1 is a cross-sectional view of one embodiment of a transdermal therapeutic drug delivery device which may be used in accordance with the present invention.

[00031] FIG. 2 is a cross-sectional view of another embodiment of a transdermal therapeutic drug delivery device which may be used in accordance with the present invention.

[00032] FIG. 3 is a cross-sectional view of yet another embodiment of a transdermal therapeutic drug delivery device which may be used in accordance with this invention.

[00033] FIG. 4 is a cross-sectional view of one embodiment of a fluid-imbibing drug delivery device which may be used in accordance with the present invention.

[00034] FIG. 5 is a DSC profile for a non-annealed ethylene vinyl acetate film comprising 9% vinyl acetate wherein the DSC profile is examined at a temperature range of -50 - 150° C heated at a rate of 10° C/min.

[00035] FIG. 6 is a DSC profile for an annealed ethylene vinyl acetate film comprising 9% vinyl acetate wherein the DSC profile is examined at a temperature range of -50 - 150° C heated at a rate of 10° C/min.

[00036] FIG. 7 is a plot of the in vitro skin flux of fentanyl from systems according to this invention with annealed and non-annealed rate controlling membranes.

[00037] FIG. 8 is a plot of the in vitro skin flux of ethanol from systems according to this invention with annealed and non-annealed rate controlling membranes.

[00038] FIG. 9 is a plot of the in vitro skin flux of fentanyl vs. the annealing temperature.

[00039] FIG. 10 is a plot depicting water uptake of annealed and non-annealed polyurethane membranes.

[00040] FIG. 11 is a plot depicting water uptake vs. annealing time of polyurethane plug membranes.

[00041] FIG. 12 is a plot depicting system weight gain vs. time for systems comprising annealed and non-annealed membranes.

[00042] FIG. 13 is a plot depicting average system release rate vs. time from systems comprising annealed and non-annealed membranes.

[00043] FIGS. 14 and 15 are plots depicting water uptake vs. annealing temperature for various polyurethane membranes at dry or 1% moisture conditions in the annealing oven.

[00044] FIG. 16 is a plot depicting the effect of annealing temperature and moisture content on the melt temperature of the hard segment of polyurethane.

DETAILED DESCRIPTION OF THE INVENTION

[00045] According to this invention, rate controlling membranes for controlled drug delivery systems are subjected to an annealing process which comprises subjecting the rate controlling membranes to an annealing temperature (T_a) for a specified time after conversion of the polymer pellet to the membrane or during the conversion process itself. The membranes are

maintained at the annealing temperature for a predetermined period of time, and subsequently cooled to ambient conditions over a time period ranging from 0.1 to 150 hours, preferably 0.1 - 48 hours. The membranes are then incorporated into a controlled drug delivery system.

[00046] Proper annealing conditions are selected in accordance with the particular polymer membrane based upon its thermal properties including its glass transition temperature, T_g, and melting point, T_m, molecular weight, molecular weight distribution, and crystallization kinetics. A wide range of annealing conditions can be selected. The annealing temperature T_a is above T_g and below T_m of the membrane material. The most rapid annealing process occurs at a T_a halfway between T_g and T_m. The largest crystal formation is observed at a T_a just below T_m. The preferred annealing temperature according to this invention is within the range of above about 30° C and at least 5° C below T_m of the polymer membrane material, more preferably about 45° C to 80° C. The membrane is preferably maintained at the annealing temperature for a period of time of about 1 to 250 hours, more preferably about 1 to 75 hours. According to a preferred embodiment, it is preferable to allow the membrane to set at room temperature for relaxation for a predetermined period prior to the annealing step.

[00047] A preferred embodiment is directed to rate controlling membranes that are more predictable with respect to thermal transients. According to this embodiment, the permeability of rate controlling membranes subjected to the annealing process of this invention is maintained below a predetermined maximum level after exposure of the system to thermal transients. Membrane annealing according to this embodiment provides predetermined delivery rates for predetermined administration intervals within an overall administration period.

[00048] A particularly preferred embodiment according to this aspect of the invention is directed to rate controlling membranes comprising an ethylene vinyl acetate (EVA) copolymer. The desired membrane permeability